I. INTRODUCTION

Sepsis is responsible for 9.3% of all deaths in the United States annually, with an incidence of over 750,000 cases, or 3 per 1000 population. The management of severe sepsis is aimed at maintenance of hemodynamic stability, identification and treatment of the infectious source, and the interruption of the inflammatory cascade resulting in septic shock. Septic, or distributive, shock results from both decreased perfusion pressure secondary to hypotension, as well as abnormal shunting of a hypermetabolic cardiac output. The ultimate goals in therapy are to eradicate the source of infection, restore effective tissue perfusion, both global and regional, and normalize cellular metabolism.

II. PURPOSE

To minimize the incidence of practice variability in surgical critical care patients through standard practice guidelines for the resuscitation of sepsis induced shock.

III. INTERVENTIONS

A. Patients with sepsis who are hypotensive (absolute SBP < 90 mmHg or >40 mmHg less than baseline SBP or MAP < 70mmHg) should be treated in an Intensive Care Unit (ICU) where they can be closely monitored. Mechanical ventilation may be required in order to maximize oxygen delivery.

B. Within the first hour of triaged diagnosis, culture data collected, antimicrobial administration, lactate level attained and fluid resuscitation for hypotension or elevated lactate. See Appendix II for diagnosis and antimicrobial guide.

C. Initial resuscitation using goal-directed therapies with isotonic crystalloids is recommended with colloid administration for patients requiring a high volume of crystalloid administration to meet resuscitation goals.

D. As resuscitation continues, it is of paramount importance to search for the septic source through the attainment of a medical history, the patient’s physical exam, cultures, and other diagnostic modalities.

E. An arterial line should be placed in all of these patients.

F. Resuscitation should continue with predetermined endpoints including the following:
   1. target mean arterial pressure (MAP) of 65 mmHg
   2. urinary output (uo) of ≥0.5 cc/kg/hr
   3. CVP of 8-12 mm Hg
4. stroke volume (SV) of 0.7cc/kg-1 cc/kg.
5. SVO2 ≥ 65% or SCVO2 ≥ 70%
6. Targeting resuscitation to normalize lactate in patients with elevated lactate levels

G. Consider invasive monitoring of hemodynamic status to assist with resuscitation. Assessment of cardiac filling pressures may require monitoring of the CVP, placement of a PA catheter, or an echocardiogram.

H. Transfuse when Hgb < 7 to a goal Hgb of 7.9 g/dl. Blood products can also be given at the clinician’s discretion if the following are present: tachycardia, oliguria, severe mixed venous oxygen desaturation, cardiac dysfunction, coronary artery disease, persistent lactic acidosis, or active bleeding.

I. Consider supplementing crystalloid resuscitation with colloid when patients require substantial amounts of crystalloid.

J. If early, aggressive fluid resuscitation does not restore MAP despite a CVP 8-12 or an echocardiogram demonstrating adequate cardiac filling, begin an infusion of Norepinephrine (Table 1). Other vasopressor combinations may also be used transiently in the face of life threatening hypotension while fluid resuscitation is ongoing.

K. Mean arterial pressure is the endpoint of vasopressor therapy. However, it is mandatory to supplement MAP with other measurements of global perfusion.

L. If Norepinephrine dose exceeds 10 mcg/min, consider adding an infusion of epinephrine at 2-10 mcg/min in addition to or potentially substituted for norepinephrine. Vasopressin may be added at 0.03-0.04 units/minute as third line to increase MAP or reduce the overall epinephrine/norepinephrine dose and should not be used as a single initial vasopressor.

M. If the patient is still hypotensive and impaired myocardial contractility is known or suspected, add an inotrope, specifically Dobutamine infusion up to 20 mcg/kg/min (Table 2). Impaired myocardial contractility is defined as decreased EF, impaired contractile response to volume loading, or low peak systolic/end-systolic volume ratio.

N. If SV is impaired, decrease vasopressor or add an inotrope.

O. Consider transthoracic echocardiogram if MAP < 65, ↓ SV, ↑ lactate, and/or ↓ urine output.

P. If septic shock is suspected, it is appropriate to start broad-spectrum antibiotics until culture results and sensitivities are back, at which time antibiotic coverage should be narrowed according to the organisms identified. Refer to UPHS Sepsis Bundle.

http://www.uphs.upenn.edu/surgery/Education/trauma/SCCS/protocols/Sepsis_Algorithm.pdf

Q. Persistent hypotension (SBP < 90 or ≥30mmHg less than baseline SBP) for greater than 1 hour which is unresponsive to fluid therapy and escalating vasopressor dosages, treat Adrenal Insufficiency empirically with Hydrocortisone (dose ≤ 200 mg/day)
1. Glucose goal < 180 mg/dL, consider insulin gtT for persistently elevated glucose >200 mg/dL.

R. Continue/Initiate other supportive therapies including: Mechanical ventilation using lung protective strategies, minimizing analgesia and sedation, moderate glucose control, DVT/PE prophylaxis, stress ulcer prophylaxis, renal replacement therapy, enteral nutrition and/or parenteral nutrition when applicable.

**Table 1: Early Vaspressors**

<table>
<thead>
<tr>
<th>Norepinephrine</th>
<th>Action</th>
<th>Therapeutic Effect</th>
<th>Dosing</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1 adrenergic agonist</td>
<td>Used to ↑ BP without causing a ↓ in CI or organ function; ↑ organ perfusion by ↑ vascular tone</td>
<td>2 + mcg/min</td>
<td>More potent than Dopamine</td>
<td></td>
</tr>
<tr>
<td>β1 + β2 adrenergic agonist but less β2 effects</td>
<td>No upper dosing limit</td>
<td>Use as first line agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1 effect is much more pronounced than β1</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Epinephrine</th>
<th>Action</th>
<th>Therapeutic Effect</th>
<th>Dosing</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1 + α2 adrenergic agonist β1 + β2 adrenergic agonist, α effects predominantly at ↑ doses</td>
<td>Used as second line therapy and possibly replace norepinephrine if clinically more effective</td>
<td>1-10- mcg/min</td>
<td>↑ lactate production and ↓ splanchnic blood flow</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vasopressin</th>
<th>Action</th>
<th>Therapeutic Effect</th>
<th>Dosing</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 receptor agonist (vascular smooth muscle)</td>
<td>↑ MAP or reduce doses of epinephrine and or norepinephrine</td>
<td>0.03 - 0.04 units/min</td>
<td>Hormonal deficiency in sepsis</td>
<td></td>
</tr>
<tr>
<td>Dose is not titrated</td>
<td>Use as physiologic replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Potent vaspressors can decrease renal blood flow. Cardiac index (CI) should be monitored and maintained at normal levels to optimize renal blood flow. Keep pulmonary vascular resistance (PVR) at the lowest values compatible for restoration of hemodynamics. Titrte vaspressors to SV in addition to MAP. In general, vaspressors may also impair splanchnic blood flow causing stress ulceration, ileus, or malabsorption.*
Table 2: Inotropes

<table>
<thead>
<tr>
<th></th>
<th>Action</th>
<th>Therapeutic Effect</th>
<th>Dosing</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>β1 + β2 receptor agonist</td>
<td>↑SV and CO</td>
<td>2.5-20 mcg/kg/min</td>
<td>First line drug if CI is &lt;2.5 or evidence of low tissue perfusion following fluid resuscitation</td>
</tr>
<tr>
<td>1st line agent</td>
<td></td>
<td>↓PCWP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓MAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>α-adrenergic agonist, β-adrenergic agonist effects</td>
<td>↑ CI</td>
<td>1-10 mcg/min</td>
<td>↑ lactate production and ↓ splanchnic blood flow</td>
</tr>
<tr>
<td>2nd line agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α-adrenergic agonist, less β-adrenergic agonist effects</td>
<td>Modest ↑ CI</td>
<td>2-12 mcg/min</td>
<td>More potent than Dopamine</td>
</tr>
</tbody>
</table>

* Titrate to keep adequate MAP, SVO₂, and urinary output.
IV. BIBLIOGRAPHY


Clinical Practice Guidelines (CPG) are meant to standardize and optimize care and decrease variability in practice. They are intended to be used as framework for the delivery of patient care in the surgical critical care units. CPG’s are a combination of evidence-based medicine and accepted practices in critical care medicine. CPG’s are intended to provide decision support for the management of the majority of patients, and are not proposed as directives, rules, or policies. They are not substitutes for clinical judgement. Deviations from the CPG’s are expected when deemed medically necessary; all exceptions should be documented in the medical record and require discussion between the Surgical Critical Care attending and the attending of the primary or consulting service.

Approved by:

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12/5/13
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Appendix I

**Resuscitation in Septic Shock**

- **Airway with mechanical ventilation**
  - No anemia / coagulopathy
  - Fluid resuscitation to pre-determined endpoints
    - Anemic / clinical S/S (F)
      - Biologically active colloids if hgb < 7: PRBC
      - > 3L
      - A-line and CVP placement. Continue resuscitation
        - CVP>8 MAP<65
          - MAP < 65
            - Add Epinephrine at 1 to 10 mcg/min
            - Check transthoracic echo
              - Goal: SV > 0.7 cc/kg - 1 cc/kg
          - Add Vasopressor 0.03-0.04 units/min
            - Inotrope - Dobutamine
            - Prolonged need for vasopressors?
              - Yes
                - Impaired myocardial contractility, rising lactate,
                  SVO2 < 60, uo < 0.5cc/kg
              - No
                - Clinical endpoints of resuscitation
          - MAP > 65
Appendix II. Infection Issues and Antimicrobial Therapy in Sepsis

I. Diagnosis
   A. 2 sets of blood cultures and other clinically indicated cultures attained before antimicrobial therapy if no significant delay (>45 minutes) in the start of antimicrobials.
   B. Imaging studies performed promptly to confirm a potential source.

II. Antimicrobial Therapy
   A. Administration of effective intravenous antimicrobials within the first hour of recognition of septic and severe sepsis without septic shock.
   B. Initial empiric anti-infective therapy based on patients history and UPHS Pharmacy Guidelines
   C. Antimicrobial regimen should be reassessed daily for potential de-escalation.
   D. Empiric combination therapy should not be administered for greater than 35 days. De-escalation to the most appropriate single therapy should be performed when susceptibilities become available.
   E. Antiviral therapy indicated as early as possible in patients with severe sepsis or septic shock of viral origin.


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